Docket No.: 205-007US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	David E. Wolf et al.	Art Unit: 1639
Serial No.:	10/632,725	Examiner: Shibuya
Filed:	August 1, 2003	Confirmation No.: 2807
Title:	METHOD OF MEASURING MOLECULAR INTERACTIONS	

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APPEAL BRIEF

Appellants submit the following brief in support of their Notice of Appeal, dated July 26, 2007, in response to the outstanding Office Action dated April 26, 2007 and the Advisory Action dated July 26, 2007.

CERTIFICATE OF TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is being electronically transmitted to the United States Patent and Trademark Office, by EFS-Web, on September 26, 2007.

Erin Margit Dajka
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Erin Margit Dajka
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I. Real Party In Interest

The real party in interest is Sensor Technologies LLC.

II. Related Appeals and Interferences

There are no related appeals or interferences pending.

III. Status of Claims

Claims 59-66, 68, and 118-138 are pending.

Claims 59-66 and 118-138 are rejected.

Claims 1-58, 67, 69, and 70-117 are cancelled.

Claim 68 is withdrawn.

Claims 59-66 and 118-138 are on appeal.

IV. Status of Amendments

There are no unentered Amendments.

V. Summary of the Claimed Subject Matter

A summary of each independent claim and each dependent claim argued separately is provided below. The support listed for each claim is exemplary, as support for the claimed subject matter can be found in general throughout Appellants' Specification.

Claim 59 is directed to a method of assaying for a pathogen in a sample, the method including exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume (Appellants' Specification, page 6, lines 18-21).

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen, and determining the presence or absence of the pathogen (*Id.*, lines 22-28, and page 7, lines 1-3).

Claim 62 depends from claim 60 and further specifies that the sample includes a plurality of unique fluorescently tagged probes, each unique probe comprising a unique fluorophore, each unique probe being capable of binding a unique pathogen (*Id.*, page 7, lines 7-9).

Claim 63 depends from claim 60 and further specifies that the sample further includes a second fluorescent tag that includes a fluorophore different from the fluorophore of the first fluorescent tag. (*Id.*, page 4, lines 14-15).

Claim 65 depends from claim 1 and specifies that the pathogen includes a bacterium (*Id.*, page 6, line 29).

Claim 66 depends from claim 60 and specifies that the pathogen comprises a virus (*Id.*, page 6, line 30).

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen (*Id.*, page 29, lines 12-15).

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe (*Id.*, page 22, lines 24-25).

Claim 126 depends from claim 124 and further specifies that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient (*Id.*, page 8, line 28-29).

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function (*Id.*, page 8, lines 21-24).

Claim 129 depends from claim 127 and further specifies that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient (*Id.*, page 8, lines 28-29).

Claim 130 depends from claim 59 and further specifies that said pathogen comprises at least one of a bacterium and a virus (*Id.*, page 6, lines 29-30).

Claim 131 depends from claim 59 and specifies that the identity of the pathogen is unknown (*Id.*, page 31, line 27).

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds (*Id.*, Examples 1-4 and FIGs. 1A-4A).

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding a unique pathogen, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen (*Id.*, page 6, lines 22-27 and page 7, lines 7-9).

VI. Grounds for Rejection to be Reviewed on Appeal

A. Whether claim 63 satisfies the criteria under 35 U.S.C. § 112, second paragraph?

B. Whether claims 132-137 satisfy the criteria under 35 U.S.C. § 112, first paragraph?

C. Whether claims 59-66 and 118-138 satisfy the criteria under 35 U.S.C. § 112, first paragraph?

D. Whether claims 59, 118-121, 124-126, 130-132, 134 and 136 satisfy the criteria under 35 U.S.C. § 112, second paragraph?

E. Whether claims 131-133 satisfy the criteria under 35 U.S.C. § 112, second paragraph?

F. Whether claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 102(e) over Rigler et al. (US 6,582,903 B1)?

G. Whether claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 102(b) over Rigler (Journal of Biotechnology, vol. 41 (1995), pp. 177-186)?

H. Whether claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 102(b) over Weiner et al. (Digestion, 2000, vol. 61, pp. 84-89)?

I. Whether claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 102(b) over Walter et al. (Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810)?

J. Whether claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 103 over Kask (US 6,515,289) in view of Lahiri et al., (US 2003/0138853 A1)?

VII. Argument

A. Claim 63 satisfies the criteria under 35 U.S.C. § 112, second paragraph.

Claim 63 stands rejected under 35 U.S.C. § 112, second paragraph.

Claim 63 depends from claim 60 and further recites, "a second fluorescent tag comprising a fluorophore different from the fluorophore of said first fluorescent tag." Claim 60 recites in relevant part, "at least one first fluorescent tag." The first fluorescent tag provides the requisite antecedent basis for the language of claim 63. Appellants submit, therefore, that claim 63 satisfies the criteria under 35 U.S.C. § 112, second paragraph, and respectfully requests that the Board overrule the same.

B. Claims 132-137 satisfy the criteria under 35 U.S.C. § 112, first paragraph.

Claims 132-137 stand rejected under under 35 U.S.C. § 112, first paragraph.

As a preliminary matter, it is well established that claim language is not required to be described in *ipsis verbis* in the Specification to satisfy the description requirement of 35 U.S.C. § 112. *See, e.g., In re Lukach,* 442 F.2d 967 (CCPA 1971); *Henry J. Kaiser Col. v. McLouth Steel Corp.,* 257 F. Supp. 372 (E.D. Mich. 1966). The test to determine whether claim language constitutes new matter is whether the application as filed clearly conveyed to those of ordinary skill in the art that Appellants invented the claimed subject matter. See, e.g., *In re Wertheim*, 541 F.2d 257, 265 (CCPA 1976). In *Wertheim*, the Patent Office objected to the addition of the language, "a particle size of at least 0.25 mm," arguing that it was new matter because the specification as originally filed disclosed a particle size of from 0.25 mm to 2.0 mm. *Id.* The Patent Office further argued that the language, "a particle size of at least 0.25 mm," contained no upper limit and therefore was not disclosed. *Id.* The *Wertheim* specification stated, "At the end of the (cooling) belt the extract is removed as a continuous rigid sheet which may then be broken up into fragments suitable for grinding. These fragments may, for example, be ground to a particle size which is preferably within the range 0.25 to 2.0 mm." *Id.* The court found that the appellant's specification did describe "a particle size of at least 0.25 mm," without an upper limit, and therefore the proposed limitation did not constitute new matter. *Id.* at 266.

Here, the Examiner objects to the inclusion of the limitation, "wherein said analyzing occurs over a period of seconds" in claims 132 and 133, and the specifying of a minimum number of seconds in claims 134-137, on the basis that this language is open-ended in duration. Appellants submit that the above-captioned application clearly conveys to those of ordinary skill in the art that Appellants invented a method in which analyzing occurs over a period of seconds, a period of at least 15 seconds and a period of at least 30 seconds. Examples 1-4 and FIGS. 1A, 2A 3A and 4A of the above-captioned application provide examples of the requisite support. Example 1 and FIG. 1A reflect the analysis of fluctuations in fluorescence that are due to the movement of two pathogens, i.e., bacteria, which passes through a confocal detection volume over a period of seconds; Example 2 and FIG. 2A reflect the analysis of fluctuations in fluorescence due to the movement of a pathogen, e.g., a single bacterium, which passes through a confocal detection volume in a period of less than 30 seconds; Example 4 and FIG. 4A reflect analyzing fluctuations of fluorescence due to the movement of a pathogen, e.g., a single bacterium, which passes through a confocal detection volume in a period of less than 15 seconds. Appellants submit, therefore, that the time periods set forth in claims 132-137 are disclosed in Appellants' Specification. Since claims 132-137 satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, Appellants submit that the rejection of claims 132-137 is unwarranted and respectfully request that the rejection be overruled.

C. Claims 59-66 and 118-138 satisfy the criteria under 35 U.S.C. § 112, first paragraph.

Claims 59-66 and 118-138 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

Claim 59 is directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. Methods for developing probes to pathogens are known. Appellants' Specification describes such methods at page 30, line 15 – page 31,

line 25. United States Provisional Application No 60/430,273, to which the above-captioned application claims priority, also contains a very detailed explanation of preparing probes for pathogens (see, e.g., Appellants' Specification, pages 5, 6, and 11-17). In addition, the Example section of the Appellants' Specification describes working examples of the method and a number of probe pathogen sets (see, e.g., *Id.*, pages 42-46). Appellants' Specification thus describes the method of claim 59.

The July 26, 2007 Advisory action states, "it is unpredictable that analysis of the diffusion or flow of, e.g., a bacteria through a subvolume, would allow identification of the bacteria as a pathogen" (July 26th Advisory action, page 8). We note that claim 59 does not recite, "identifying a bacteria as a pathogen." To the contrary, claim 59 is directed to a method of assaying for a pathogen in a sample. In light of the above, Appellants submit that claim 59 satisfies the written description requirement in that it describes the method of claim 59, which can be carried out regardless of the probe or the pathogen. As such, Appellants' Specification satisfies the criteria under 35 U.S.C. § 112, first paragraph. Accordingly, Appellants respectfully request that the rejection be overruled.

Claims 60-66 and 118-138 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, for at least the same reasons set forth above with respect to claim 59. Accordingly, Appellants respectfully request that the rejection of claims 60-66 and 118-138 under 35 U.S.C. § 112, first paragraph, be overruled.

Claims 60-66, 68, 122, 123, 127-129, 133, 135 and 137

Claims 60-66, 68, 122, 123, 127-129, 133, 135 and 137 also satisfy the written description requirement for at least the following additional reasons.

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen, and determining the presence or absence of the pathogen. Thus, the probe of claim 60 is known to bind a certain pathogen. Appellants' specification describes methods of assaying for the presence of a pathogen in a sample using a known probe. For at least

this additional reason, the rejection of claim 60 under 35 U.S.C. § 112, first paragraph, is unwarranted and Appellants respectfully request that it be overruled.

Claims 61-66, 68, 122, 123, 127-129, 133, 135 and 137 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, for at least the same reasons set forth above with respect to claim 60.

Claim 129

Since there are no other rejections outstanding against claim 129, Appellants respectfully request that the Board enter a finding that claim 129 is allowable.

D. Claims 59, 118-121, 124-126, 130-132, 134 and 136 satisfy the criteria under 35 U.S.C. § 112, second paragraph.

Claims 59, 118-121, 124-126, 130-132, 134 and 136 stand rejected under 35 U.S.C. § 112, second paragraph.

Appellants have previously requested clarification of this rejection. MPEP 2172.01 states:

> A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. § 112, first paragraph, as not enabling. In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). See also MPEP § 2164.08(c). Such essential matter may include missing elements, steps or necessary structural cooperative relationships of elements described by the applicant(s) as necessary to practice the invention.
>
> In addition, a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 U.S.C. § 112, second paragraph, for failure to point out and distinctly claim the invention. See *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976); In re Collier, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). *But see Ex parte Nolden*, 149 USPQ 378, 380 (Bd. Pat. App. 1965) ("[I]t is not essential to a patentable combination that there be interdependency between the elements of the claimed device or that all the elements operate concurrently toward the desired result"); *Ex parte Huber*, 148 USPQ 447, 448-49 (Bd. Pat. App. 1965) (A claim does not

necessarily fail to comply with 35 U.S.C. § 112, second paragraph where the various elements do not function simultaneously, are not directly functionally related, do not directly intercooperate, and/or serve independent purposes.) (Emphasis added.)

Although the Examiner's reasoning as set forth in the July 26th Advisory action at page 9, para. 14, utilizes language and reasoning that sounds in 35 U.S.C. § 112, first paragraph, since the rejection is asserted to be based on 35 U.S.C. § 112, second paragraph, Appellants address the rejection as written, i.e., under the second paragraph of Section 112.

Claim 59 is directed to a method of assaying for a pathogen in a sample, the method including exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. The July 26th Advisory action states, "The instant rejection could be overcome by a final step drawn to 'thereby assaying for a pathogen in the sample'." Advisory action, page 9, final paragraph. Such a phrase is not necessary. It is clear that the method steps set forth in claim 59 are for the method recited in the preamble --they could be for no other method. Moreover, the preamble states, "a method of assaying for a pathogen in a sample." Accordingly, Appellants submit that the rejection of claims 59, 118-121, 124-126, 130-132, 134 and 136 under 35 U.S.C. § 112, second paragraph, is unwarranted, and respectfully request that it be overruled.

E. Claims 131-133 satisfy the criteria under 35 U.S.C. § 112, second paragraph.

Claims 131-133 stand rejected under 35 U.S.C. § 112, second paragraph.

Claim 131

Claim 131 depends from claim 59 and further specifies that the identity of the pathogen is unknown. The April 26th Office action asserts, "[T]he language.. [,] 'identity of said pathogen is unknown,' appears to read upon a mental step." April 26th Office action, page 12. The term "unknown" is well-known throughout all fields of science. It

is a common term used to refer to something that is not known. The phrase, "identity of said pathogen is unknown" refers to a fact --not a mental step. The identity of the pathogen in the sample is unknown at the time the method is conducted. Such a sample might be taken, for example, from a city's water supply. In the event that citizens of that city had become sick and the water supply was suspected, one could take a sample of the water, without knowing whether or not it contained a pathogen, and analyze it according to the method of claim 131. In this example, if a pathogen is present, the identity of that pathogen is unknown at the time the method is conducted. Appellants submit that claim 131 satisfies the criteria of 35 U.S.C. § 112, second paragraph, that the rejection of claim 131 under 35 U.S.C. § 112, second paragraph, is unwarranted, and respectfully request that the Board overrule the same.

Claims 132 and 133

Claims 132 and 133 depend from claims 59 and 60, respectively and further specify that the analyzing occurs over a period of seconds. A second is a known unit of time. There is nothing indefinite about a second or a period of seconds. Claims 132 and 133 inform the skilled artisan that an analysis that does not extend over a period of seconds does not fall within the claim language. In other words, an analysis that occurs in less than a second, or over a period of one second, does not fall within the claims. Likewise, an analysis that occurs over a plurality of seconds falls within the claim. The skilled artisan would readily understand both the term "seconds" and the metes and bounds of the method of claims 132 and 133. Appellants submit, therefore that the rejection of claims 132 and 133 under 35 U.S.C. § 112, second paragraph, is unwarranted and respectfully request that it be overruled by the Board.

F. Claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 102(e) over Rigler et al. (US 6,582,903 B1).

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(e) over Rigler et al.

Rigler et al. disclose a method for identifying one or a small number of molecules in very small volumes (i.e., 10^{-14} to 10^{-17} liters) using a laser excited fluorescence correlation spectroscopy (Rigler et al., col. 3, lines 21-25). (Emphasis added.) Rigler et

al. explain that an object of their invention is a method for identifying one or a small number of molecules (*Id.*, col. 1, lines 7-8; see also, col. 1., line 65-col. 2, line 6). Rigler et al. further disclose, "[I]t would be more advantageous if analytic methods were sufficiently sensitive to qualitatively and quantitatively apply directly to single molecules or ensembles of a few molecules" (*Id.* lines 20-23). (Emphasis added.) Rigler et al. are particularly interested in studying the interactions that occur between molecules at the molecular level including biochemical reactions, equilibrium constants, and rate constants of single molecules (*Id.*, col. 5, lines 22-26). According to Rigler et al., the illuminated area of the Rigler et al. device has an approximate dimension of 0.1 μm^2, and the measuring volume of the Rigler et al. device is about 1000 times smaller than the measuring volumes described in the literature (*Id.*, col., 3, lines 28-32). A very small measuring volume is important to Rigler et al. because it allows for the dwell time of a molecule in the measuring volume to be about 1000 times shorter than in conventional systems and thereby enables equilibrium constants and rate constants of specific biological recognition reactions to be measured (*Id.* at lines 47-55). Riger et al. further explain, "[The] ligand [that] is to be observed does not change[,] or changes but hardly[,] its molecular structure during its entering into the measuring compartment and its leaving the same." *Id.*, lines 43-46. Rigler et al. also disclose that they have attained a signal-to-noise ratio of 1000, which is necessary for measuring single molecules (*Id.*, col. 5, lines 1-3). Rigler et al. further explain that the deterioration of this ratio follows the third power of the increased radius of the measuring volume (r^3). In other words, as the measuring volume increases, the signal-to-noise ratio decreases.

Rigler et al. explain that problems in the art include the fact that the observation element was so large that biologically interesting molecules having low translational diffusion coefficients were present in the observation element for a period of about 50 ms (*Id.*, col. 3, lines 3-5). Such a period, according to Rigler et al., is significantly too large because it causes strong bleaching of the respective dye ligands serving as the luminophore (*Id.* at lines 5-7). The Rigler et al. method relies on frequent excitation of the luminophore. According to Rigler et al., frequent excitation increases the chemical reactivity of the luminophorous structure towards molecules of the environment, in particular oxygen, whereby the luminescence is altered or quenched (*Id.* at lines 7-11).

Rigler et al. refer to this as photobleaching and further explain that photobleaching leads to false measuring data (*Id.* at lines 11-14). Rigler et al. also disclose that the measuring period over which their analysis is conducted is no greater than 500 milliseconds (ms) (see *Id.*, Abstract), and that the average dwell time for the small volume elements of their invention is less than 1 millisecond (*Id.*, col. 7, lines 23-25). Rigler et al. further explain that the average measuring time for one measurement ranges between 10 ms and 100 ms, which enables specific biological interactions to be measured (*Id.*, lines 51-59).

In distinguishing their method from a cell sorter, Rigler et al. explain that on the level of a cell, their method is able to distinguish between different molecules bearing chromophores and being present in the measuring volume, whereas in the cell sorter the concentration of the chromophore is determined irrespective of whether it is part of a small molecule, occurs in a complex or is bound to a cell (*Id.*, col. 12, lines 54-61). Rigler et al. go on to explain that for slowly diffusing complexes such as cell cultures or tissues, the translational diffusion of the complexes is irrelevant for the analysis (*Id.*, col. 21, lines 56-62). In other words, the complex appears as if it is stationary, i.e., it is effectively stationary, for purposes of the Rigler et al. analysis.

> Surprisingly, even cells can be measured in aqueous suspension despite their large masses. Brownian motion and turbulences are sufficiently high to move, e.g., a membrane segment with its receptors[,] into the measuring volume and out again without intervening bleaching phenomena of the dye labels occurring. Schematic FIG. 5 depicts the measurement of nearly stationary molecules according to the invention. As indicated by the rectangle, for instance, they may be present as membrane receptors on an immobilized cell (rectangle). The coordinate axes illustrate the analysis, according to the invention, of non-fluctuating molecules as well by forced relative motion of the measuring volume with respect to the stationary element. This can be done by a relative change of the laser coordinates, of the coordinates of the measuring volume, or of the coordinates of the sample volume, or of a combination thereof.
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> The procedure described according to the invention is possible in the case that the time of translational diffusion of the slowly diffusing complex is irrelevant for

> analysis and rather the absolute or relative number of the dye labels linked thereto is of interest. This is the case, for instance, in determining receptor binding constants on cell cultures or in tissues.

Id., col. 21, lines 22-61.

Claim 59

Claim 59 is directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. In addition, the method must be shown in the reference "'in as complete detail as contained in the .... claim.'" M.P.E.P. 2131 *quoting Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Rigler et al. seek to analyze single molecules. A pathogen is an organism. Rigler et al. are not interested in analyzing pathogens. Appellants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Appellants' Specification, page 33, lines 5-6). Appellants' Specification expressly discloses,

> Other suitable targets include organisms including e.g., pathogens (e.g., bacterial, viral, rickettsia), pathogen components, toxins, and macromolecules associated with an organism. Examples of pathogen components include pathogens, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

This evidence from the record clearly demonstrates that Appellants intended the term "pathogen" to refer to an organism, and to convey the idea that while a pathogen necessarily includes a component of a pathogen, a component of a pathogen is not inherently a pathogen or an organism. Since the lack of this evidence was the only basis on which the rejection of claim 59 under 35 U.S.C. § 102(e) over Rigler et al. was maintained, and this evidence is clearly of the record, Appellants submit that the rejection

of claim 59 under 35 U.S.C. § 102(e) over Rigler et al. has been overcome and respectfully request that it be withdrawn.

The Rigler et al. reference is further deficient for at least the following additional reasons. Although Rigler et al. mention viruses and bacteria, Rigler et al. are interested in the interactions of molecules (*see, e.g.,* Rigler et al., col. 1, lines 7-8; see also, col. 1., line 65-col. 2, line 6). This is demonstrated by Rigler et al.'s various discussions pertaining to cells. In particular, Rigler et al. disclose that they are interested in the receptors on membrane segments of cells, (*see, Id.*, col. 21, lines 24-27), as well as receptor binding constants on cell cultures or in tissues (*see, Id.*, col. 21, lines 59-61). In the system depicted in FIG. 5 of Rigler et al., e.g., the cell is immobilized (*see, Id.*, lines 29-31). Rigler et al. are interested in activity that is happening at the receptors of the cell and analyzes various segments of the membrane to study this activity. Thus, the mere use of the terms "pathogen," "virus" and "bacterium" in Rigler et al. does not constitute a teaching of a method that includes analyzing the fluctuations of the fluorescence due to diffusion or flow of a pathogen through a subvolume. To the contrary, many things associated with a pathogen, virus, or bacterium could theoretically be analyzed. Rigler et al. must expressly teach analyzing the fluctuations of the fluorescence due to the diffusion or flow of a pathogen through a subvolume to establish a case of *prima facie* anticipation, and they do not. Again, Rigler et al. do not measure the diffusion or flow of a pathogen. Rather, Rigler et al. look at activity that is occurring on cell receptors and membranes --not at the activity of entire organisms. It is telling that the July 26th Advisory action fails to cite a passage from Rigler et al. establishing anything to the contrary.

The July 26th Advisory action takes the position that "the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen." July 26th Advisory action, page 14, first full paragraph. Regardless as to whether this statement is true or not, claim 59 expressly requires the presence of a pathogen, and further requires analyzing the fluctuations of fluorescence that are due to the diffusion or flow of a pathogen –not a pathogen component. Rigler et al. do not teach analyzing the fluctuations of fluorescence that are due to the diffusion or flow of a pathogen. Thus, Rigler et al. fail to teach each and every element of claim 59. Thus, the rejection of claim

59 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand, and Appellants respectfully request that the Board overrule the same.

Claims 60-66, 118-125, 127, 128 and 130-133 are distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons set forth above in distinguishing claim 59.

Claims 60, 65, 66, 130, 132 and 133 are further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the following additional reasons.

Claim 60

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen, and determining the presence or absence of the pathogen. As established above, Rigler et al. do not teach assaying for the presence of a pathogen in a sample, or analyzing fluctuations of fluorescence that are due to the diffusion or flow of a pathogen. Rigler et al. also do not teach determining the presence or absence of the pathogen in a sample. Instead Rigler et al. discuss analyzing molecules and molecular interactions. Molecules are not pathogens. Thus, analyzing molecules does not constitute analyzing a pathogen -- let alone analyzing fluctuations of fluorescence that are due to the diffusion or flow of a pathogen. The July 26th Office action indicates that column 8, lines 25-30 of Rigler et al. discloses determining the presence or absence of a pathogen in a sample. The cited passage discloses that the Rigler et al. method is applicable to DNA/RNA analysis (see, Rigler et al., col. 8, lines 23-29). DNA, itself, is not a pathogen, and analyzing DNA does not inherently constitute identifying the presence or absence of a pathogen. Moreover, nothing in such a disclosure constitutes a teaching of a probe capable of binding a predetermined pathogen. Rigler et al. thus fail to teach each and every element of the method of claim 60. Accordingly, for at least this additional reason, the rejection of claim 60 under 35 U.S.C. § 102(e) is unwarranted and Appellants respectfully request that it be overruled.

Claims 65, 66 and 130

Claim 65 depends from claim 1 and specifies that the pathogen includes a bacterium. Rigler et al. do not teach analyzing fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Rather, Rigler et al. analyze the interaction of molecules in their subvolume and, in particular, the binding constants of molecules, equilibrium constants of molecules, dissociation rate constants of complexes, and conformational changes in biological macromolecules (Rigler et al., col. 7, line60-col. 8, line 24). Rigler et al. expressly disclose that their method is for the fluorescence spectroscopy of single molecules, molecular complexes and molecular fragments (*Id.*, col. 6, lines 8-11) and further expressly admonish that because single molecules, molecular complexes and molecular fragments are their target, it is "critical ... that there be a confocally located pinhole aperture having an extremely small orifice in the beam path of the [excitation] radiation." *Id.*, lines 11-15. Rigler et al. thus not only fail to teach analyzing fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through their subvolume, but also provide no reason to the skilled artisan to do so.

The July 26th Advisory action appears to refer to the passage at column 6, lines 46-60 of Rigler et al. as support for the rejection of claim 65. The cited passage does not, however, expressly teach analyzing the fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Rather, the cited passage merely refers to the dwell time of a bacterium in Rigler et al.'s measuring volume. It cannot be disputed that the disclosure of a dwell time does not constitute an express teaching of analyzing the fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume, as required by claim 65. Moreover, because Rigler et al. expressly disclose that they seek to obtain information on the molecular activity that occurs on cell surfaces and membranes, there is no basis for inferring that a reference to a bacterium's dwell time somehow constitutes an inherent teaching of analyzing the fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Again, for anticipation to exist, the method must be shown in the reference "in as complete detail as contained in the claim. M.P.E.P. 2131 *quoting Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Rigler et al. thus fail to teach

each and every element of the method of claim 65. Accordingly, the rejection of claim 65 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand, and Appellants respectfully request that it be overruled.

Claims 66 and 130 are further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the additional reasons set forth above in distinguishing claim 65.

Claim 120

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen. Rigler et al. do not teach a probe that includes multiple binding sites for binding a pathogen. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 120 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 120 under 35 U.S.C. § 102(e) over Rigler et al. is unwarranted and respectfully request that it be overruled.

Claim 123 is further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the reasons set forth above in distinguishing claim 120.

Claim 121

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe. Rigler et al. do not teach a pathogen that includes multiple binding sites for binding a probe. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 121 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 121 under 35 U.S.C. § 102(e) over Rigler et al. is unwarranted and respectfully request that it be overruled.

Claim 127

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Rigler et al. do not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 127 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim

127 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand and respectfully request that it be overruled.

Claims 132 and 133

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. The measuring period over which the Rigler et al. analysis is conducted is no greater than 500 milliseconds (see Rigler et al., Abstract). Rigler et al. further disclose that the average measuring time for one measurement ranges between 10 ms and 100 ms (*Id.*, col. 7, lines 51-53). Rigler et al. also explain that the average dwell time in the subvolume for complexes of interest to them is less than 1 millisecond, and that for virtually all of the complexation reactions of interest to them, the complex will remain stable throughout its dwelling time in the measuring volume (*Id.*, col. 7, lines 23-27). There is no express teaching in Rigler et al. of analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample. In addition, Rigler et al. fail to teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a period of seconds. The Examiner does not dispute this. Instead, the Examiner takes the position that "[a] 'period of seconds' encompasses time periods less than one second." July 26th Advisory action, page 15, first full paragraph. The Examiner cites no authority for this position. Therefore, the record fails to establish a *prima facie* case of anticipation of claim 132 over Rigler et al. For at least this additional reason, the rejection of claim 132 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand and Appellants respectfully request that it be overruled.

Claim 133 is further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons set forth above in distinguishing claim 132.

Claims 138, 62 and 118

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one

pathogen. To establish a *prima facie* case of anticipation of a claim, a single prior art reference must teach each and every element of the claimed composition. In addition, the method must be shown in the reference "'in as complete detail as contained in the .... claim.'" M.P.E.P. 2131 *quoting Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Rigler et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. The Examiner takes the position that "Rigler ... teach parallel determination of at least two different analytes in at [*sic*] sample, reading on a plurality of probes." *Id.* Claim 138 does not merely require the presence of a plurality of probes. Rather, claim 138 requires a plurality of probes each of which is capable of binding to a unique pathogen. It cannot be disputed that the above-quoted passage from Rigler et al. does not constitute a teaching of the method of claim 138 in as complete detail as contained in claim 138. Therefore, Rigler et al. fail to teach each and every element of the method of claim 138, and a *prima facie* case of anticipation of claim 138 has not been established. Accordingly, the rejection of claim 138 under 35 U.S.C. § 102(e) over Rigler et al. cannot stand and Appellants respectfully request that it be overruled.

Claims 62 and 118 are further distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons set forth above in distinguishing claim 138.

G. Claims 59-64, 66, 118-125, 127, 128, 130-133, and 138 are patentable under 35 U.S.C. § 102(b) over Rigler (Journal of Biotechnology, vol. 41 (1995), pp. 177-186).

Claims 59-64, 66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(b) over Rigler.

Rigler discloses methods for analyzing molecular interactions between ligands and target molecules by exciting a sample to fluorescence with a laser beam and correlating the fluctuations of molecular intensity. Rigler indicates that FCS can be used to examine molecular interactions such as hybridization between nucleic acid primers and DNA or RNA targets, between peptide ligands and cell-bound receptors, and between antigen and antibodies (see, e.g., Rigler, Abstract). Rigler describes the detection of a typical biological interaction of a fluorescence labeled DNA primer of 18 nucleotides

binding to a target DNA molecule, namely single stranded M13 bacteriophage DNA (*Id.*, page 178-179).

Claim 59

Claim 59 is directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Rigler is directed to single molecule detection (see, e.g., Rigler, Title). Rigler explains that the improvements in fluorescence correlation spectroscopy have allowed single molecules to be recorded in fractions of milliseconds (*Id.*, page 177-178). Rigler is interested in interactions between ligands and target molecules (*Id.*, page 178). Rigler describes analyzing free and DNA-bound primer. DNA-bound primer is not a pathogen, as required by claim 59. A pathogen is an organism. DNA- bound primer is not an organism. Appellants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Appellants' Specification, page 33, lines 5-6). This is clear evidence from the record that Appellants intended the term "pathogen" to refer to an organism. Moreover, according to the Examiner's definition, a pathogen is a "disease producing microorganism or material" (July 26th Advisory action, page 17). There is no evidence of record that single stranded M13 bacteriophage DNA, itself, produces a disease. Accordingly, the record fails to establish that Rigler teaches a sample volume that includes a pathogen.

Rigler further fails to teach analyzing the fluctuations of fluorescence due to diffusion or flow of a pathogen through a subvolume and is not interested in doing so. Rigler is directed to single molecule detection (see, e.g., Rigler, Title). Rigler explains that the improvements in fluorescence correlation spectroscopy have allowed single molecules to be recorded in fractions of milliseconds (*Id.*, page 177-178). Rigler is interested in interactions between ligands and target molecules (*Id.*, page 178). Rigler is not interested in analyzing the fluctuations of fluorescence due to diffusion or flow of a pathogen through a subvolume. Rigler thus fails to teach each and every element of the

method of claim 59. The rejection of claim 59 under 35 U.S.C. § 102(b) over Rigler thus cannot stand and Appellants respectfully request that it be overruled.

Claims 60-66, 118-125, 127, 128, 130-133 and 138 are distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons set forth above in distinguishing claim 59.

Claims 60, 62, 65, 66, 118, 130, 132, 133, and 138 are further distinguishable over Rigler for at least the following additional reasons.

Claim 60

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen, and determining the presence or absence of the pathogen. Rigler does not teach a probe capable of binding a pathogen. Rather Rigler discloses that FCS can be used to analyze interactions between ligands and target molecules that differ in size and lists antigen and antibody and DNA-primer and DNA-target as examples thereof (Rigler, page 178). DNA-primers are not inherently probes capable of binding a predetermined pathogen. Accordingly, Rigler fails to teach each and every element of the method of claim 66. Appellants submit, therefore, that the rejection of claim 66 under 35 U.S.C. § 102(b) over Rigler cannot stand, and respectfully request that it be overruled.

Claims 66 and 130

Claim 66 depends from claim 1 and specifies that the pathogen comprises a virus. Rigler does not teach a virus. Rigler also does not analyze fluctuations of fluorescence that are due to the diffusion or flow of a virus through a subvolume. Rigler is directed to single molecule detection (see, e.g., Rigler, Title). Rigler explains that the improvements in fluorescence correlation spectroscopy have allowed single molecules to be recorded in fractions of milliseconds (*Id.*, page 177-178). Rigler is interested in interactions between ligands and target molecules. *Id.*, page 178. Rigler describes analyzing free and DNA-bound primer. Rigler does not teach analyzing the fluctuations of fluorescence due to diffusion or flow of a pathogen that is a virus through a subvolume and is not interested

in doing so. Rigler thus fails to teach a required element of claim 66. The Examiner takes the position that the disclosure at page 182, column 2 of Rigler provides the requisite teaching. Such is not the case. Rigler disclose,

> Here the possibility to detect a single molecule opens up new scenarios. Like a single organic dye molecule also single virus molecules containing RNA or DNA sequences can be made visible by incorporating fluorescence markers in a specific way. This can be achieved by hybridization of the vital DNA or RNA with several fluorescence labeled primers in the form of a cocktail or by replication of the vital DNA/RNA with fluorescence lapelled nucleotides and an unlabelled specific primer.

This passage does not teach analyzing fluctuations of fluorescence that are due to the diffusion or flow of a virus through a subvolume. To the contrary, in this passage Rigler describes labeling DNA or RNA and analyzing the labeled DNA or RNA –not the virus itself. Accordingly, a *prima facie* case of anticipation of claim 66 has not been made and the rejection of claim 66 under 35 U.S.C. § 102(b) over Rigler cannot stand. Appellants respectfully request that it be overruled.

Claim 130 is further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the additional reasons set forth above in distinguishing claim 66.

Claim 120

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen. Rigler does not teach a probe that includes multiple binding sites for binding a pathogen. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 120 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 120 under 35 U.S.C. § 102(b) over Rigler is unwarranted and respectfully request that it be overruled.

Claim 123 is further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the reasons set forth above in distinguishing claim 120.

Claim 121

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe. Rigler does not teach a pathogen that includes multiple binding sites for binding the probe. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 121 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 121 under 35 U.S.C. § 102(b) over Rigler is unwarranted and respectfully request that it be overruled.

Claim 127

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Rigler does not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 127 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim 127 under 35 U.S.C. § 102(b) over Rigler cannot stand and respectfully request that it be overruled.

Claims 132 and 133

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. The fluorescence correlation spectroscopy system of Rigler includes an illuminated and detected volume of 0.2 femtoliters (Rigler, page 178, second column). Rigler discloses that a single organic dye molecule, when excited to fluorescence, can be recorded in fractions of milliseconds (Rigler, page 178). Rigler also discloses that a single Rhodamin 6G molecule can be detected within 100 microseconds and less (*Id.*, page 181, first column). Rigler also explains that an autocorrelation function can be obtained within 0.1 second when a ligand labeled receptor is present in a concentration of 1 nanomole. Figure 7 of Rigler depicts obtaining the autocorrelation function of M13-DNA over a period of less than 300 seconds. Rigler further explains that for particles with diffusion coefficients and diffusion times similar to those of M13 bacteriophage DNA, the detection time will be a limiting factor if particle detection rests

on thermal motion only. To solve this problem, Rigler discloses using electric field gradients to achieve an analysis time of less than 100 microseconds (*Id.*, page 183). Rigler thus teaches away from analyzing fluctuations in fluorescence due to the diffusion over a period seconds. The Examiner takes the position that "[the] term 'period of seconds' encompasses time periods of less than one second. July 26th Advisory action, page 18. The Examiner cites no authority for this position. Rigler thus also fails to teach at least this additional element of the method of claim 132. Accordingly, a *prima facie* case of anticipation of claim 132 has not been made. Thus the rejection of claim 132 under 35 U.S.C. § 102(b) over Rigler cannot stand and Appellants respectfully request that it be withdrawn.

Claim 133 is further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons set forth above in distinguishing claim 132.

Claims 138, 62 and 118

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. To establish a *prima facie* case of anticipation of a claim, a single prior art reference must teach each and every element of the claimed composition. In addition, the method must be shown in the reference "'in as complete detail as contained in the .... claim.'" M.P.E.P. 2131 *quoting Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Rigler does not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. Nothing in the record establishes anything to the contrary. Rigler thus fails to teach each and every element of the method of claim 138. The Examiner takes the position that "Rigler ... teaches [the] use of several fluorescence labeled primers in the form of a 'cocktail', thereby teaching a plurality of probes." July 26th Advisory action, page 18, third full paragraph. Claim 138 does not merely require the presence of a plurality of probes. Rather, claim 138 requires a plurality of probes each of

which is capable of binding to a unique pathogen. It cannot be disputed that the above-quoted passage from Rigler does not constitute a teaching of the method of claim 138 in as complete detail as contained in claim 138. Accordingly, a *prima facie* case of anticipation of claim 138 has not been made. Appellants submit, therefore, that the rejection of claim 138 under 35 U.S.C. § 102(b) over Rigler cannot stand, and respectfully request that it be withdrawn.

Claims 62 and 118 are further distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons set forth above in distinguishing claim 138.

H. Claims 59-64, 66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 102(b) over Weiner et al. (Digestion, 2000, vol. 61, pp. 84-89).

Claims 59-64, 66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 102(b) over Weiner et al. (Digestion, 2000, vol. 61, pp. 84-89).

Weiner et al. describe a preliminary evaluation of fluorescence correlation spectroscopy for serum hepatitis C virus RNA quantification (Weiner et al., page 85, first column). More specifically, Weiner et al. describe extracting HCV RNA from human serum, and performing cDNA synthesis and PCR using a Cy3-labeled fluorescent probe to HCV RNA (*Id.*). Weiner et al. also disclose diluting the PCR mixtures, denaturing the mixtures to resolve nonspecific binding of the fluorescence-labeled probes, and analyzing the crude PCR mixtures with an argon-ion laser fluorescence correlation spectrometer to determine the diffusion times of free Cy3-labeled primers (*Id.*, pages 85-86). Weiner et al. further determined the amount of fluorescence-labeled hepatitis C virus amplimers in a given PCR mixture (*Id.*).

Claim 59 is directed to a method of assaying for a pathogen in a sample where the sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Appellants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Appellants' Specification, page 33, lines 5-6). The term "pathogen" as used in claim 59 thus refers to an organism. Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which

is a macromolecule. Weiner et al. do not teach a method of measuring levels of hepatitis C virus. Hepatitis C virus RNA is not an organism. Thus, the RNA of hepatitis C virus is not a pathogen. The Examiner takes the position that a pathogen is any disease producing microorganism or material (July 26th Advisory Action, page 19). Weiner et al. do not teach that the RNA of hepatitis C virus, itself, produces a disease. There is no evidence of record establishing anything to the contrary. Therefore, the RNA of hepatitis C virus also is not a material that produces a disease. Weiner et al. thus fail to teach a sample that includes pathogen. Weiner et al. also fail to teach analyzing the fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume of the sample. Weiner et al. thus fail to teach required elements of the method of claim 59. The rejection of claim 59 under 35 U.S.C. § 102(b) over Weiner et al. thus is unwarranted, and Appellants respectfully request that it be overruled.

Claims 60-64, 66, 118-125, 127, 128, 130-133 and 138 are distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 59.

Claims 60, 66, 130, and 132-138 are further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 60.

Claim 60

Claim 60 is further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the following additional reasons. Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. As has been established above, Weiner et al. do not teach a method of assaying for the presence of a pathogen. Weiner et al. also do not teach determining the presence or absence of a pathogen in a sample. Weiner et al. further fail to teach a probe capable of binding a predetermined pathogen. Instead, Weiner et al. discloses reversely transcribed hepatitis C RNA with Cy3-labeled

oligonucleotide primers (Weiner et al., pages 85-86 and Fig. 1). Cy3-labeled oligonucleotide primers reversely transcribed with hepatitis C RNA are not probes that are inherently capable of binding a predetermined pathogen. Weiner et al. thus fail to teach each and every element of the method of claim 60. Accordingly, Appellants submit that the rejection of claim 60 under 35 U.S.C. § 102(b) over Weiner et al. has been overcome and respectfully request that it be withdrawn.

Claims 61-64, 66, 122, 123, 127, 128 are further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 60.

Claims 66 and 130

Claim 66 depends from claim 60 and specifies that the pathogen comprises a virus. Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of PCR amplified hepatitis C virus RNA, which is a macromolecule. Neither the RNA of hepatitis C virus nor the amplified hepatitis C virus RNA is a virus. Thus, Weiner et al. do not teach a virus. There is no evidence of record establishing anything to the contrary. Weiner et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a virus through a subvolume. To the contrary, Weiner et al. are studying PCR amplified RNA. PCR amplified RNA is not a virus. Weiner et al.thus fail to teach each and every element of the method of claim 66. Appellants submit, therefore, that the rejection of claim 66 under 35 U.S.C. § 102(b) over Weiner et al. cannot stand, and respectfully request that it be overruled.

Claim 130 is further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the additional reasons set forth above in distinguishing claim 66.

Claim 120

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen. Weiner et al. do not teach a probe that includes multiple binding sites for binding a pathogen. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 120 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 120 under 35 U.S.C. § 102(b) over Weiner et al. is unwarranted and respectfully request that it be overruled.

Claim 123 is further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the reasons set forth above in distinguishing claim 120.

Claim 121

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe. Weiner et al. do not teach a pathogen that includes multiple binding sites for binding the probe. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 121 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 121 under 35 U.S.C. § 102(b) over Weiner et al. is unwarranted and respectfully request that it be overruled.

Claim 127

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Weiner et al. do not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 127 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim 127 under 35 U.S.C. § 102(b) over Weiner et al. cannot stand and respectfully request that it be overruled.

Claims 132-137

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. Weiner et al. do not teach analyzing fluctuations in fluorescence due to diffusion or flow of a pathogen over a period of seconds. To the contrary, Weiner et al. analyze PCR products that include Cy3-labeled amplimers. Cy3-labeled amplimers are not pathogens. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 132 has not been made and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim 132 under 35 U.S.C. § 102(b) over Weiner et al. is unwarranted and respectfully request that it be overruled.

Claims 133-137 are distinguishable under 35 U.S.C. § 103 over Weiner et al. for at least the same reasons as set forth above in distinguishing claim 132.

Claims 138, 62 and 118

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. To establish a *prima facie* case of anticipation of a claim, a single prior art reference must teach each and every element of the claimed composition. In addition, the method must be shown in the reference "'in as complete detail as contained in the .... claim.'" M.P.E.P. 2131 *quoting Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Weiner et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. The Examiner takes the position that "Weiner ... teach the use of internal control RNAs labeled with different fluorochromes to be processed in the FCS assay for pathogen, thereby reading on a plurality of unique fluorescently tagged probes" (July 26th Advisory action, page 21). Claim 138 does not merely require the presence of a plurality of probes. Rather, claim 138 requires a plurality of probes each of which is capable of binding to a unique pathogen. It cannot be disputed that RNA's labeled with different fluorochromes do not constitute unique probes capable of binding to a unique pathogen. Furthermore, the above-quoted passage from Weiner et al. does not constitute a teaching of the method of claim 138 in as complete detail as contained in claim 138. Accordingly, a *prima facie* case of anticipation of claim 138 has not been made, and the rejection of claim 138 under 35 U.S.C. § 102(b) over Weiner et al. cannot stand. Appellants respectfully request that it be overruled.

Claims 62 and 118 are further distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 138.

I. Claims 59-65, 118-125, 127, 128, and 130-138 are patentable under 35 U.S.C. § 102(b) over Walter et al. (Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810).

Claims 59-65, 118-125, 127, 128, and 130-138 stand rejected under 35 U.S.C. § 102(b) over Walter et al.

Walter et al. discuss methods for combining an amplification technique, namely PCR, with fluorescence correlation spectroscopy to detect the specific *in vitro* amplifications of the genomic sequence of a bacterium (Walter et al., Abstract). Walter et al. describe using at least one primer, a rhodamine-labeled fluorescent probe, and *Mycobacterium tuberculosis* genomic DNA as a target (*Id.*). Walter et al. also disclose the use of fluorescence correlation spectroscopy to measure the diffusion times of fluorescently labeled nucleic acids (*Id.*, page 12809).

As set forth above, claim 59 is directed to a method of assaying for a pathogen in a sample that includes a least one pathogen, at least one probe, and at least one fluorescent tag. The method of claim 59 also includes analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. Walter et al. do not teach a sample that includes a pathogen. To the contrary, Walter et al. disclose combining an amplification technique, namely PCR, with an FCS-based detection technique. Walter et al. disclose PCR amplification of Mycobacterium tuberculosis genomic DNA with the Stoffel fragment of Thermus aquaticus DNA polymerase in the presence of nanomolar concentrations of a rhodamine-labeled probe (Walter et al., Abstract). Walter et al. test different primer/probe combinations on *Mycobacterium tuberculosis* genomic DNA as a target (Walter et al., Abstract). (Emphasis added.) Appellants' Specification expressly lists a pathogen as an example of an organism (See, e.g., Appellants' Specification, page 33, lines 5-6). The genomic DNA of *Mycobacterium tuberculosis* is not an organism. According to the Examiner's definition, a pathogen is a "disease producing microorganism or material" (July 26th Advisory action, page 17). The genomic DNA of *Mycobacterium tuberculosis*, itself, does not produce a disease, and nothing in the record establishes anything to the contrary. Therefore the genomic DNA of *Mycobacterium tuberculosis* is not a pathogen.

Walter et al. also do not analyze the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. Rather, Walter et al. measure the diffusion times of fluorescently labeled nucleic acids and probe extensions --labeled nucleic acids and probe extensions are not organisms, do not produce a disease, and, therefore, are not pathogens. Walter et al. thus fail to teach each and every element of the method of claim 59. Appellants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 102(b) over Walter et al. is unwarranted and respectfully request that the Board overrule the same.

Claims 60-65, 118-125, 127, 128, and 130-138 are distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons set forth above in distinguishing claim 59.

Claims 60, 61-64, 65, 122, 123, 127, 128, 130, 132, 133, and 138 are further distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the following additional reasons.

Claims 60, 61-64, 122, 123, 127, and 128

Claim 60 is directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Walter et al. do not assay for the presence of a pathogen. Rather, Walter et al. analyze properties associated with probe extensions that result from hybridization. Walter et al. also do not teach analyzing fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Rather, Walter et al. analyze fluctuations in fluorescence associated with fluorescently labeled nucleic acids and probe extensions. Nucleic acids and probe extensions are not organisms and do not inherently produce a disease. Nucleic acids and probe extensions thus are not pathogens. Walter et al. thus not only fail to teach a pathogen, but also fail to teach analyzing fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Walter et al. also do not teach determining the presence or absence of a pathogen in a sample.

Walter et al. thus fail to teach each an every element of the method of claim 60. Accordingly, the rejection of claim 60 under 35 U.S.C. § 102(b) over Walter et al. is unwarranted and Appellants respectfully request that it be overruled.

Claims 61-64, 122, 123, 127, and 128 are distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons set forth above in distinguishing claim 60.

Claim 65

Claim 65 depends from claim 60 and specifies that the pathogen comprises a bacterium. Walter et al. analyze properties associated with probe extensions that result from hybridization. A probe extension that results from hybridization is not inherently a bacterium. Thus, Walter et al. do not teach a bacterium. Walter et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a bacterium through a subvolume. Nothing in the record establishes anything to the contrary. Walter et al. thus fail to teach a required element of claim 65. Accordingly, a *prima facie* case of anticipation of claim 65 has not been made. Appellants submit, therefore, that the rejection of claim 65 under 35 U.S.C. § 102(b) over Walter et al. cannot stand, and respectfully request that it be overruled.

Claim 120

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen. Walter et al. do not teach a probe that includes multiple binding sites for binding a pathogen. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 120 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 120 under 35 U.S.C. § 102(b) over Walter et al. is unwarranted and respectfully request that it be overruled.

Claim 123 is further distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the reasons set forth above in distinguishing claim 120.

Claim 121

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe. Walter et al. do not teach a pathogen that includes multiple binding sites for binding the probe. Nothing in the record establishes

anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 121 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 121 under 35 U.S.C. § 102(b) over Walter et al. is unwarranted and respectfully request that it be overruled.

Claim 127

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Walter et al. do not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of anticipation of claim 127 has not been made, and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim 127 under 35 U.S.C. § 102(b) over Walter et al. cannot stand and respectfully request that it be overruled.

Claim 130

Claim 130 depends from claim 59 and specifies that the pathogen comprises at least one of a bacterium and a virus. Walter et al. analyze properties associated with probe extensions that result from hybridization. A probe extension that results from hybridization is not inherently a bacterium or a virus. Thus, Walter et al. do not teach a bacterium or a virus. Walter et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a bacterium or a virus through a subvolume. Nothing in the record establishes anything to the contrary. Walter et al. thus fail to teach a required element of claim 130. Accordingly, a *prima facie* case of anticipation of claim 130 has not been made. Appellants submit, therefore, that the rejection of claim 130 under 35 U.S.C. § 102(b) over Walter et al. cannot stand, and respectfully request that it be overruled.

Claims 132 and 133

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. Walter et al. disclose that after the PCR amplification of Mycobacterium tuberculosis genomic DNA with the Stoffel fragment of Thermus aquaticus DNA polymerase in the presence of nanomolar concentrations of a rhodamine-

labeled probe, the mobility of the rhodamine-labeled probe can be monitored during a 30 second measurement using a fluorescence correlation spectroscopy device (Walter et al., Abstract). Monitoring fluorescently labeled nucleic acids and probe extensions does not constitute analyzing the fluctuations of the fluorescence due to diffusion or flow of a pathogen through the subvolume, and further fails to constitute analyzing the fluctuations of the fluorescence due to diffusion or flow of a pathogen through the subvolume over a period of seconds. Therefore, for at least this additional reason Walter et al. fail to teach the method of claim 132. Appellants submit, therefore, that the rejection of claim 132 under 35 U.S.C. § 102(b) over Walter et al. cannot stand, and respectfully request that it be overruled.

Claim 133 is further distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons set forth above in distinguishing claim 132.

Claims 138, 62 and 118

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, and measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence, and determining the presence or absence of at least one pathogen. To establish a *prima facie* case of anticipation of a claim, a single prior art reference must teach each and every element of the claimed composition. In addition, the method must be shown in the reference "'in as complete detail as contained in the .... claim.'" M.P.E.P. 2131 *quoting Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Walter et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as required by claim 138. The Examiner takes the position that "Walter ... teaches multiplex analysis with different labeled probes, which read [*sic*] on a plurality of unique fluorescently-tagged probes" (July 26th Advisory action, page 24). Claim 138 does not merely require the presence of a plurality of probes. Rather, claim 138 requires a plurality of probes each of which is capable of binding to a unique pathogen. It cannot be disputed that the above-quoted passage from Walter et al. does not constitute a teaching

of the method of claim 138 in as complete detail as contained in claim 138. Accordingly, a *prima facie* case of anticipation of claim 138 has not been made. Walter et al. also do not teach determining the presence or absence of at least one pathogen. Nothing in the record establishes anything to the contrary. Walter et al. thus fail to teach each and every element of the method of claim 138, and a *prima facie* case of anticipation of claim 138 has not been made. Accordingly, the rejection of claim 138 under 35 U.S.C. § 102(b) over Walter et al. cannot stand and Appellants respectfully request that it be overruled.

Claims 62 and 118 are further distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons set forth above in distinguishing claim 138.

J. Claims 59-66, 118-125, 127, 128, 130-133 and 138 are patentable under 35 U.S.C. § 103 over Kask (US 6,515,289) in view of Lahiri et al., (US 2003/0138853 A1).

Claims 59-66, 118-125, 127, 128, 130-133 and 138 stand rejected under 35 U.S.C. § 103 over Kask in view of Lahiri et al.

Kask discloses a method for characterizing a sample on the basis of intermediate statistical data (Kask, col. 1, lines 5-6). The method of Kask includes monitoring intensity fluctuations of radiation emitted by molecules or particles by detecting sequences of photon counts, determining an intermediate statistical function from a probability function of at least two arguments, and determining a distribution of molecules or particles as a function of at least two specific physical properties (*Id.*, col. 2, lines 47-63). Kask also refers to a method of identifying nucleic acid strands by a labeled probe molecule and a method that uses a mixture of primers labeled with dyes of different brightness to identify a target nucleic acid (*Id.*, col. 8, lines 18-29).

Lahiri et al. disclose an array that includes a plurality of biological membrane microspots on a surface of a substrate (Lahiri et al., Abstract). The microspots include a protein bound to the membrane (Lahiri et al., [0006]). The array of Lahiri et al. is produced, used and stored in an environment exposed to air under ambient or controlled humidities (*Id.*, [0006]. Lahiri et al. expressly state the array is not used in an aqueous environment (*Id.*). The method of Lahiri et al. can be used for detecting a binding event between a probe array and target compounds (*Id.* at [0023]). Lahiri et al. disclose that the

target can be labeled and the method can include a step in which the presence of the label is detected (*Id.*, [0023]). Lahiri et al. explain that the array can be interfaced with optical detection methods (*Id.*, [0071]).

Claim 59 is directed to a method of assaying for a pathogen in a sample. The method includes exciting a sample with radiation, measuring the fluorescence from a subvolume of the sample, and analyzing the fluctuations of the fluorescence due to the diffusion or flow of the pathogen through the subvolume, where the sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*,127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). Rather, to establish a *prima facie* case of obviousness based upon a proposed combination of references there must be a reason in the prior art to combine the references. See, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. _____ (2007). Evidence of a reason to combine can be found if there is a teaching, suggestion or motivation in the prior art for making the proposed combination. See, M.P.E.P. 2142; *Fromson v. Anitec Printing Plates, Inc.*, 132 F.3d 1437 (Fed. Cir. 1997); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, (Fed. Cir. 1998). The reason, teaching, suggestion or motivation to make the claimed combination must be found in the prior art and must not be based on Appellants' disclosure. See, M.P.E.P. 2142. Here there is no such reason, teaching, suggestion or motivation.

It is undisputed that Kask fails to teach a sample that includes a pathogen (see April 26th Office action, page 23). Kask is further deficient in that he also does not teach analyzing the fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. The method of Kask requires monitoring intensity fluctuations of radiation emitted by molecules or particles (Kask, col. 2, lines 52-53). The Kask method characterizes a sample on the basis of intermediate statistical data. The focus of Kask is on his intermediate statistical function. Kask seeks to utilize his function for measuring slight differences in the physical properties of various species. Throughout Kask there are references to "units." Kask discloses that the term "unit of a sample" refers, in general, to

> subparts of a sample which are capable of emitting, scattering and/or reflecting radiation. A sample might contain a number of identical units or different units which preferably can be grouped into species. The term "different species" refers also to different states, in particular different conformational states, of a unit such as a molecule. Fluorescently labelled or naturally fluorescent molecules, molecular complexes, vesicles, cells, beads and other particles in water or other liquids may be examples of fluorescent units in liquid samples, while examples of fluorescent units of a solid sample are impurity molecules, atoms or ions, or other fluorescence centers.

Id., col. 3, lines 40-52. Kask also provides a laundry list of examples of "units," which includes "particles, molecules, aggregates, vesicles, cells, viruses, bacteria, centers or mixtures thereof in solids, liquids or gases." *Id.*, col. 6, lines 31-34. Kask also discloses a number of specific physical properties that can characterize a "unit," including absorption cross-section, quantum yield of fluorescence, diffusion coefficient, correlation time of radiation intensity fluctuations, any other property expressing how fast or slow Brownian motion of a given unit is, specific brightness, polarization ratio, anisotropy, any other property expressing the extent of polarization of fluorescence, lifetime of fluorescence, and ratio of fluorescence intensity passing through different optical filters. See, e.g., Kask, col. 3, lines 53-62, col. 6, line 55-col. 7, line 36. Although Kask mentions that the units can be bacteria or viruses, Kask does not teach or suggest characterizing a virus or bacterium with any specific physical property. In particular, Kask does not teach that the specific physical property for characterizing a virus or bacterium is analyzing the fluctuations in fluorescence due to the diffusion or flow of a bacterium or virus through a subvolume.

In the background section and throughout the patent, Kask explains that fluorescence correlation spectroscopy is for use in studying molecules (*Id.*, col. 1, lines 23-36). Kask also discuses uses of his method, all of which involve analyzing molecular interactions. For example, with respect to cells and vesicles, Kask discloses,

> [S]ubstances that are possibly pharmacologically active can be analyzed through their interaction with specific receptors by examining said interaction with binding of a luminescently labeled ligand to receptors wherein natural receptors

> on their carrier cells as well as receptors on receptor-overexpressing carrier cells or receptors on vesicles or receptors in the form of expressed molecules or molecular complexes may be used.

Id., col. 7, lines 43-50.

In the above-quoted passage, Kask does not teach analyzing the fluctuations in fluorescence due to the diffusion of the cell or vesicle. Rather, Kask is interested in interactions with receptors on the cell or vesicle. The above-quoted passage thus demonstrates that Kask is looking at interactions that are occurring at the molecular level. This is further demonstrated by the fact that all of the examples and all of the claims of Kask involve analyzing radiation emitted by molecules. None of the examples of Kask involve analyzing bacteria or viruses, in general, or analyzing the diffusion or flow of a bacterium or virus, in particular.

The fact that some of the claims of Kask mention that a sample includes a bacteria or a virus is of no moment. The claims of Kask that mention a bacteria or a virus do not state that the bacteria or virus is the molecule or particle referred to in the independent claim from which it depends. Likewise, the fact that some claims of Kask mention fluctuations is irrelevant. Those claims of Kask do not teach or suggest that the fluctuations are due to the diffusion or flow of the pathogen through the subvolume, and further fail to teach or suggest analyzing fluctuations in fluorescence due to the diffusion or flow of the pathogen through the subvolume. Therefore, Kask provides the skilled artisan with no reason to analyze fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume.

Lahiri et al. do not cure the deficiencies of Kask. As a preliminary matter, Lahiri et al. do not teach a sample that includes a pathogen. Lahiri et al. refer to a pathogen at paragraph [0077]. However, this reference is with respect to Lahiri et al.'s biological membrane array, which is the focus of the Lahiri et al. patent. In particular, Lahiri et al. disclose,

> The array may be used in a diagnostic manner when the plurality of analytes being assayed are indicative of a disease condition or the presence of a pathogen in an organism. In such embodiments, the sample which is delivered to

> the array will then typically be derived from a body fluid or a cellular extract from the organism.

Lahiri et al., [0077]. (Emphasis added.) Lahiri et al. do not teach that the sample includes a pathogen. Rather, Lahiri et al. explain that their array can be used when the analytes being assayed are indicative of a disease condition or the presence of a pathogen. Analytes that are indicative of a disease condition or the presence of a pathogen are not inherently, i.e., necessarily, pathogens. Thus, Lahiri et al. do not teach that actual pathogens are being analyzed or that actual pathogens are in the sample. Accordingly, the proposed combination of Kask and Lahiri et al. lacks a required element of claim 59, i.e., a sample that includes pathogen.

Lahiri et al. are further deficient in that the focus of Lahiri et al. is on arrays of biological membranes. In the method of Lahiri et al., a target is detected when it becomes immobilized on a biological membrane. Lahiri et al. are concerned with detecting this immobilized target. Lahiri et al. are not concerned with the diffusion of the target in general, or the diffusion of a pathogen in particular. To the contrary, any target detected by Lahiri et al. is immobilized on the Lahiri et al. membrane and therefore is incapable of diffusing. The Kask method, in contrast, relies on mobile molecules. Thus, the skilled artisan familiar with Kask would have no reason to look to Lahiri et al., and further would find Lahiri et al. to have no bearing on the method of Kask.

The fact that Lahiri et al. disclose that their biological membrane array can be interfaced with a number of detection methods, and then list fluorescence correlation spectroscopy as one example of such a detection method, is of no moment (see, Lahiri et al., para. [0071]). Nothing in such a disclosure specifically directs the skilled artisan to employ fluorescence correlation spectroscopy in combination with a pathogen --let alone to analyze the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample. Therefore, the skilled artisan would have no reason to do so. Moreover, Lahiri et al. seek to immobilize a pathogen on their array. Accordingly, the skilled artisan would refrain from event attempting to analyze the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample, because the pathogen of Lahiri et al. would not be diffusing or flowing. Appellants submit, therefore, that the proposed combination of Kask and Lahiri et al. fails to render

obvious the method of claim 59, and respectfully request that the rejection of claim 59 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. be overruled.

Claims 60-66, 118-125, 127, 128, and 130-138 are distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the same reasons as set forth above in distinguishing claim 59.

Claims 62, 118, 120, 121, 127, 128, and 130-138 are further distinguishable over Kask in view of Lahiri et al. for at least the following additional reasons.

Claims 62 and 118

Claim 62 depends from claim 60 and further specifies that the sample includes a plurality of unique fluorescently tagged probes, each unique probe comprising a unique fluorophore, each unique probe being capable of binding a unique pathogen. Kask does not teach a sample that includes a pathogen, let alone a plurality of unique fluorescently tagged probes capable of binding a unique pathogen. To the contrary, Kask discloses that the dyes all bind to the same target (Kask, col. 8, lines 18-29).

Lahiri et al. do not cure the deficiencies of Kask. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 62 has not been made. Appellants submit, therefore, that the rejection of claim 62 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be overruled.

Claim 118 is further distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the reasons set forth above in distinguishing claim 62.

Claim 120

Claim 120 depends from claim 59 and further specifies that the probe includes multiple binding sites for binding the pathogen. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests a probe that includes multiple binding sites for binding a pathogen. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 120 has not been made and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 120 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be overruled.

Claim 123 is further distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the reasons set forth above in distinguishing claim 120.

Claim 121

Claim 121 depends from claim 59 and further specifies that the pathogen includes multiple binding sites for binding the probe. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests a pathogen that includes multiple binding sites for binding the probe. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 121 has not been made and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claims 121 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be overruled.

Claim 126

Claim 126 depends from claim 124 and further specifies that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests that the correction algorithm adjusts the measured correlation function based on a bleed through coefficient. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 126 has not been made and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim 126 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. cannot stand and respectfully request that it be overruled. There being no other substantive rejection against claim 126, Appellants submit that it is in condition for allowance and respectfully request a ruling in accordance therewith.

Claim 127

Claim 127 depends from claim 60 and further includes obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 127 has not been made and the burden has not shifted to Appellants to rebut the

same. Appellants submit, therefore, that the rejection of claim 127 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. cannot stand and respectfully request that it be overruled.

Claims 132-137

Claim 132 depends from claim 59 and further specifies that the analyzing occurs over a period of seconds. Neither Kask nor Lahiri et al. nor the combination thereof teaches or suggests analyzing the fluctuations in fluorescence that are due to the diffusion or flow of a pathogen over a period of seconds. In particular, nothing directs the skilled artisan to select a pathogen for analysis, to decide to analyze the diffusion or flow of the pathogen through a sample volume, and then to analyze the fluctuations in fluorescence for a period of seconds. Nothing in the record establishes anything to the contrary. Accordingly, a *prima facie* case of obviousness of claim 132 has not been made and the burden has not shifted to Appellants to rebut the same. Appellants submit, therefore, that the rejection of claim 132 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. is unwarranted and respectfully request that it be overruled.

Claims 133-137 are distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the same reasons as set forth above in distinguishing claim 132.

Claim 138

Claim 138 is directed to a method of assaying for the presence of a pathogen in a sample, the method including 1) exciting the sample with radiation, the sample including a plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen, 2) measuring the fluorescence from a subvolume of the excited sample, 3) analyzing the fluctuations of the fluorescence, and 4) determining the presence or absence of at least one pathogen. Kask does not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen. Rather, Kask discloses a mixture of different primers that include one or more dye molecules and are complementary to a section of the target molecule, i.e., a single target molecule, --not a number of different target molecules (see, Kask, col. 8, lines 18-29). Claim 138 does not merely require the presence of a plurality of probes. Rather, claim

138 requires a plurality of probes each of which is capable of binding to a unique pathogen.

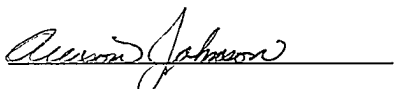
Lahiri et al. do not cure the deficiencies of Kask. Lahiri et al. do not teach or suggest a sample that includes plurality of unique fluorescently tagged probes, each unique probe including a unique fluorophore, each unique probe being capable of binding to a unique pathogen. Nothing in the record establishes anything to the contrary. The proposed combination of Kask and Lahiri et al. thus lacks a required element of the method of claim 138. Accordingly, the rejection of claim 138 under 35 U.S.C. § 103 over Kask in view of Lahiri et al. cannot stand and Appellants respectfully request that it be overruled.

The claims now pending in the application are in condition for allowance. Appellants respectfully request that the Board overrule the rejections of record with instructions to pass the application to Issue.

Please charge any fees owing or credit any over payments made to Deposit Account No. 501,171.

Respectfully submitted,

Date: September 26, 2007



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CLAIMS APPENDIX

59. A method of assaying for a pathogen in a sample, said method comprising:

exciting said sample with radiation, said sample comprising

at least one pathogen;

at least one probe, and

at least one fluorescent tag;

measuring the fluorescence from a subvolume of said excited sample; and

analyzing the fluctuations of said fluorescence that are due to the diffusion or flow of said pathogen through said subvolume.

60. A method of assaying for the presence of a pathogen in a sample, said method comprising:

exciting said sample with radiation, said sample comprising

at least one probe capable of binding a predetermined pathogen, and

at least one first fluorescent tag;

measuring the fluorescence from a subvolume of said excited sample;

analyzing the fluctuations of said fluorescence that are due to the diffusion or flow of said pathogen, when present, through said subvolume; and

determining the presence or absence of said pathogen.

61. The method of claim 60, further comprising identifying said pathogen.

62. The method of claim 60, wherein said sample comprises a plurality of unique fluorescently tagged probes, each unique probe comprising a unique fluorophore, each unique probe being capable of binding to a unique pathogen.

63. The method of claim 60, wherein said sample further comprises a second fluorescent tag comprising a fluorophore different from the fluorophore of said first fluorescent tag.

64. The method of claim 60, wherein said analyzing comprises at least one of determining the crosscorrelation function of said sample and determining the autocorrelation function of said sample.

65. The method of claim 60, wherein said pathogen comprises a bacterium.

66. The method of claim 60, wherein said pathogen comprises a virus.

118. The method of claim 59, wherein said sample comprises a plurality of unique fluorescently tagged probes, each unique probe comprising a unique fluorophore, each unique probe being capable of binding to a unique pathogen

119. The method of claim 59, wherein further comprising determining the crosscorrelation function of said pathogen.

120. The method of claim 59, wherein the probe comprises multiple binding sites for binding the pathogen.

121. The method of claim 59, wherein the pathogen comprises multiple binding sites for binding the probe.

122. The method of claim 60, further comprising determining the crosscorrelation function of said pathogen.

123. The method of claim 60, wherein the probe comprises multiple binding sites for binding the predetermined pathogen.

124. The method of claim 59 further comprising obtaining a measured correlation function of the pathogen and applying a correction algorithm to the measured correlation function.

125. The method of claim 124, wherein the measured correlation function comprises an autocorrelation function and a crosscorrelation function.

126. The method of claim 124, wherein the correction algorithm adjusts the measured correlation function based on a bleed through coefficient.

127. The method of claim 60 further comprising obtaining a measured correlation function of said pathogen and applying a correction algorithm to the measured correlation function.

128. The method of claim 127, wherein the measured correlation function comprises an autocorrelation function and a crosscorrelation function.

129. The method of claim 127, wherein the correction algorithm adjusts the measured correlation function based on a bleed through coefficient.

130. The method of claim 59, wherein said pathogen comprises at least one of a bacterium and a virus.

131. The method of claim 59, wherein the identity of said pathogen is unknown.

132. The method of claim 59, wherein said analyzing occurs over a period of seconds.

133. The method of claim 60, wherein said analyzing occurs over a period of seconds.

134. The method of claim 59, wherein said analyzing occurs over a period of at least 15 seconds.

135. The method of claim 60, wherein said analyzing occurs over a period of at least 15 seconds.

136. The method of claim 59, wherein said analyzing occurs over a period of at least 30 seconds.

137. The method of claim 60, wherein said analyzing occurs over a period of at least 30 seconds.

138. A method of assaying for the presence of a pathogen in a sample, said method comprising:

exciting said sample with radiation, said sample comprising a plurality of unique fluorescently tagged probes, each unique probe comprising a unique fluorophore, each unique probe being capable of binding to a unique pathogen; and

measuring the fluorescence from a subvolume of said excited sample;

analyzing the fluctuations of said fluorescence; and

determining the presence or absence of at least one pathogen.

EVIDENCE APPENDIX

(NONE)

RELATED PROCEEDINGS APPENDIX

(NONE)